REMARKS

Claims 25-55 are pending. Claims 1-24 were cancelled in Applicants' First Preliminary Amendment filed on April 14, 2006. Claims 25 and 28 have been amended. Claims 42 and 43 are cancelled.

Claim 25 has been amended to further define the preparations as containing a magnesium salt and/or a calcium salt. Such preparations are not disclosed or suggested in the prior art cited. Support for this amendment is found throughout the specification and in particular at original claim 4 (current claim 28), Examples 5 and 6, as well as the paragraph bridging pages 6 and 7 of the specification.

As an initial matter, it is believed the amendments may be properly entered at this time, i.e. after final rejection, pursuant to 37 CFR §1.116, because the amendments do not require a new search or raise any new issues, and they reduce issues for appeal. Indeed, it is respectfully submitted that the within amendments place the application in condition for allowance. Thus, entry of the amendments at this time is earnestly solicited.

Rejections under 35 U.S.C. §103(a)

For the sake of brevity, these rejections are summarized below and addressed in combination.

Claims 25-26, 29-30 and 35-55 remain rejected under 35 U.S.C. §103(a) over Malvolti (WO 03/004005).

Claims 25-26, 29-30 and 36-55 remain rejected under 35 U.S.C. §103(a) over Montgomery (U.S. 6,083,922).

Claims 27-28 and 31-33 remain rejected under 35 U.S.C. §103(a) over Malvolti et al. as applied to claims 25-26, 29-30 and 35-55, and further in view of Wiedmann et al. (U.S. 5,747,001).

Claim 34 remains rejected under 35 U.S.C. §103(a) over Malvolti et al. as applied to claims 25-26, 29-30 and 35-55 and further in view of Azria et al. (U.S. 5,759,565).

The rejections are traversed. None of the cited documents, even in the stated combination, teach or suggest the features of the present invention in any manner sufficient to sustain any one of the rejections.

A discussion of the references and their respective deficiencies was presented in Applicants response to the Office Action dated July 3, 2007.

Claim 25 and dependent claims 26-41 and 44-55 have been amended to further define the preparations as containing a magnesium salt and/or a calcium salt. None of Malvolti, Montgomery, Wiedmann, or Azria, either alone or in combination teach or suggest such preparations.

That is, the prior art cited does not teach or suggest "a sterile, liquid preparation in the form of an aqueous solution for application as an aerosol containing about 80 mg/ml to 120 mg/ml of tobramycin and an acidic adjuvant, wherein the preparation comprises not more than 2 mg/ml of sodium chloride and the preparation further contains a magnesium salt and/or a calcium salt" as required by claim 25 and dependent claims 26-41 and 44-55

No reasonable expectation of success in arriving at the claimed invention. Unexpected Results.

Applicants submit that even if either of the Malvolti et al. reference or the Montgomery et al. reference is combined with knowledge available to one of skill in the

art at the time of the invention to present a *prima facie* case of obviousness with respect to the instant claims (which it does not), one of skill in the art would not have a reasonable expectation of success in arriving at the invention as claimed. That is, the claims require "a sterile, liquid preparation in the form of an aqueous solution for application as an aerosol containing about 80 mg/ml to 120 mg/ml of tobramycin and an acidic adjuvant, wherein the preparation comprises not more than 2 mg/ml of sodium chloride and the preparation further contains a magnesium salt and/or a calcium salt." It is submitted that such a formulation would not be reasonably predictable from either of the references in combination with knowledge available to one of skill in the art, in view of what was known in the art as of the filing date of the application (discussed herein).

As demonstrated by the Clinical Study results (Exhibit A) and the Nebulisation Test results (Exhibit B) presented hereinbelow, the presence of magnesium salt and/or calcium salt in the claimed preparation provides unexpected improvements in inhalation therapy and aerosol generation.

Clinical Study

The clinical study described in the attached "Clinical Study Results" (Exhibit A) compares a tobramycin preparation according to the present invention (which contains a magnesium and a calcium salt) to the TOBI® reference formulation (which contains the same components as the formulation described in Montgomery (US patent 6,083,922)). The study, performed in cystic fibrosis patients infected with *Pseudomonas aeruginosa,* determined the concentration of tobramycin in the plasma and sputum of the patients as a result of aerosolisation and inhalation of the two formulations described above.

It is desirable to obtain a high concentration of tobramycin in the sputum because that is where the active agent produces its antibiotic effect. In contrast, the tobramycin concentration in the plasma should be low to minimize systemic side effects.

The clinical test results presented in Exhibit A demonstrate the following:

- treatment with the claimed preparation resulted in a higher sputum concentration of tobramycin as compared to the TOBI® reference preparation;
- treatment with the claimed preparation resulted in a lower plasma concentration of tobramycin than the TOBI® reference preparation, and
- patients that received 50% less of the claimed preparation as compared to the TOBI® reference preparation via nebulisation had a similar dose of the claimed preparation deposited in their lungs as compared to patients treated with 50% more of the TOBI® reference preparation.

More specifically, the lung dose, the higher sputum concentration and the lower plasma concentration of tobramycin that results from nebulisation of the claimed preparation, demonstrates that tobramycin has a significantly improved affinity for sputum when formulated in the claimed composition comprising a magnesium salt and/or a calcium salt, than when incorporated in the reference formulation. Nebulisation of the claimed compound is advantageous as compared to the reference formulation because 1) the higher sputum concentration produces a greater therapeutic effect, and 2) the lower plasma concentration reduces side effects of tobramycin due to tobramycin circulating in the blood.

These results demonstrate that the claimed preparation which comprises a magnesium and/or a calcium salt, in addition to sodium chloride, has unexpected advantages over the preparations known in the prior art as of the filing date of the instant application.

Although it may be known from the prior art that calcium might reduce the adhesion of *Pseudomonas aeruginosa* to the lung surface (see Tsang *et al.*, Eur. Resp. 2003, 21, 932-938; copy attached, Exhibit C) one of skill in the art would not have predicted that the inclusion of a magnesium and/or a calcium salt, in addition to sodium chloride, would significantly improve the inhalation therapy and aerosol generation of preparations of tobramycin for aerosol administration known in the prior art.

The higher affinity for sputum is associated with the presence of calcium and magnesium salts in the claimed preparations discovered by the Applicants. Indeed, this finding was later confirmed (see, e.g., Sanders *et al.*, Thorax 2006; 61:962-968; Exhibit D; a report published after the priority date of the present application, according to which the affinity of rhDNase for sputum is higher when sputum contains a distinct concentration of magnesium).

The Clinical Study presented herein demonstrates clearly that the claimed, novel tobramycin formulation for inhalation, wherein the sodium chloride concentration is reduced in favor of calcium and magnesium salts, produces significant, unexpected effects. The affinity of tobramycin for sputum colonized by bacteria such as *Pseudomonas aeruginosa* in the claimed preparations is increased thereby enhancing the therapeutic effect. Furthermore, the concentration of tobramycin in plasma is reduced, which reduces the risk of systemic side effects.

Nebulisation Test

Further advantages of the preparation according to the invention are shown in the attached "Nebulisation Test Results" (Exhibit B). This test compares the nebulisation of the claimed preparation with the TOBI® reference formulation using the same type of nebuliser (PARI eFlow®). In this test, output (i.e. percentage of tobramycin actually aerosolized), output rate, droplet size and droplet size distribution parameters were measured.

The output obtained with the preparation according to the present invention (99.35 %) was found to be higher than the output (97.49 %) obtained with the reference formulation (which corresponds to the formulation disclosed by Montgomery).

The Montgomery reference suggests that the reduction of sodium chloride concentration increases the output when nebulising tobramycin formulations with an ultrasonic nebuliser. This implies that the reduction of ion concentration (or osmolality) in the solution has a positive effect on the output. However, as a calcium and magnesium

salt have been included in the claimed formulation, the osmolality of the novel formulation is higher (0.221 Osmol/kg) than the osmolality of the reference formulation (0.170 Osmol/kg). Thus, in contrast to the suggestion by Montgomery, it has been unexpectedly found that the novel formulation produces a higher output despite the higher osmolality of the formulation compared to the reference formulation.

Additionally, the average mass median aerodynamic diameter (MMAD) of the novel formulation is slightly smaller than the MMAD measured when the formulations are nebulised. Furthermore, the fraction of droplets ≤ 5 µm and ≤ 3 µm (fine particle fraction or FPF) is 5.4% and 7.6% higher, respectively, when nebulising the novel formulation with an eFlow® nebuliser as when nebulising the reference formulation with the same nebuliser. Similar conclusions can be drawn from Figure 1 of the attached "Nebulisation Test Results" (Exhibit B).

Thus, the novel formulation is surprisingly advantageous in generating higher fractions of inhalable droplets (i.e. droplets ≤ 3 µm for children and ≤ 5 µm for adults) in comparison to the reference formulation. The effects of sodium chloride concentration and osmolality on the generated droplet size distribution has not been shown in cited prior art.

The data presented herein demonstrate that the reduction of the sodium chloride concentration in favor of calcium and magnesium salts induced several unexpected advantages, that were independent of the type of nebuliser that was used. In particular, and in contrast to the suggestions by Montgomery, the claimed formulation produced a higher output despite its higher osmolality. Furthermore, it was found surprisingly that nebulisation of the claimed formulation increased the inhalable fraction of the generated droplets. Therefore, the novel formulation has unexpected advantages that lead to a higher deposition efficiency of the active agent in the lungs.

In view of all of the above, reducing the sodium chloride concentration in favor of calcium and magnesium salts, according to the present invention, and as claimed by

claim 25 and dependent claims thereof, causes unexpected advantageous effects. First, unexpected advantages were found regarding local and systemic distribution of the drug, and second unexpected advantages with respect to physical aerosol properties were found when nebulising the claimed formulation.

Even if the references are combined, they do not provide the invention as claimed.

Moreover, Applicants submit that even if the Malvolti et al. reference or the Montgomery et al. reference were combined with knowledge available to one skilled in the art as of the time of the invention, the combination would lack essential elements of the claimed invention. Likewise, despite any such combination, one of skill in the art would not have a reasonable expectation of success in arriving at the invention as claimed.

Applicants submit that the motivation to prepare "a sterile, liquid preparation in the form of an aqueous solution for application as an aerosol containing about 80 mg/ml to 120 mg/ml of tobramycin and an acidic adjuvant, wherein the preparation comprises not more than 2 mg/ml of sodium chloride and the preparation further contains a magnesium salt and/or a calcium salt" is found in Applicants' disclosure, rather than in the combination of either of Malvolti et al. or Montgomery et al. with the knowledge of one of skill in the art.

Applicants respectfully assert that it would not have been obvious to one of ordinary skill in the art that lower concentrations of sodium chloride in combination with magnesium salt and/or calcium salt would be beneficial. **Indeed, there is nothing in the prior art which supports this contention.**

None of the preparations of tobramycin for aerosol administration described in the prior art contain a magnesium salt and/or a calcium salt and there is no reason to

assume that such a preparation would be advantageous over the preparations known in the prior art.

No motivation to combine references

Further, it is submitted that one of skill in the art would not be motivated to combine the teachings of either Malvolti et al. or Montgomery et al. with any prior art so as to successfully arrive at the invention recited in the instant claims because none of Malvolti et al., Montgomery et al., the prior art or combinations thereof, teach or suggest these essential elements of the claims.

Even assuming *arguendo* that the cited references were combined, they still fail to provide the invention as claimed.

For instance, to establish a *prima facie* case of obviousness the Examiner must identify the reason why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed. (Memo from Margaret A. Focarino Deputy Commissioner for Patent Operations to Technology Center Directors, May 3, 2007). "Often it will be necessary…to look to the interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, to determine whether there was an **apparent reason** to combine the known elements in the fashion claimed by the patent at issue. To facilitate review, this analysis **should be made explicit**." (*KSR, Int'l Co. v. Teleflex, Inc.*, 127 S. Ct., 1727, slip opinion at 14) Emphasis added "In view of the guidance provided by the Supreme Court in KSR, an examiner must continue to articulate a reason or rationale to support an obviousness rejection under 35 U.S.C. 103." (Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 in View of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.*)

For at least the reasons set forth herein, Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case of obviousness under the requirements of 35 U.S.C. § 103(a). To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or **motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings** (*In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)). Second, there must be a **reasonable expectation of success**. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on Applicants' disclosure. Finally, the prior art reference (or references when combined) must teach or suggest **all the claim limitations**. *In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (C.C.P.A. 1974).

In view of all of the above, Applicants respectfully submit that the invention according to claim 25 and dependent claims thereof is not obvious because there is nothing in the cited art that teaches or suggests that a preparation of tobramcyin containing a magnesium salt and/or a calcium salt would demonstrate significant improvements over the preparations known in the prior art. That is, neither of Malvolti et al. or Montgomery et al. teaches or suggests "a sterile, liquid preparation in the form of an aqueous solution for application as an aerosol containing about 80 mg/ml to 120 mg/ml of tobramycin and an acidic adjuvant, wherein the preparation comprises not more than 2 mg/ml of sodium chloride and the preparation further contains a magnesium salt and/or a calcium salt" as required by the instant claims.

Turning now to the rejection over Malvolti et al. and further in view of Wiedmann et al. (U.S. 5,747,001), the following remarks are offered.

Applicants respectfully traverse the rejection.

Wiedemann et al. (US Patent No 5,747,001) was described previously in Applicants response to the Office Action dated July 3, 2007.

As discussed above, the Malvolti et al. reference fails to teach or suggest "a sterile, liquid preparation in the form of an aqueous solution for application as an aerosol containing about 80 mg/ml to 120 mg/ml of tobramycin and an acidic adjuvant, wherein the preparation comprises not more than 2 mg/ml of sodium chloride and the preparation further contains a magnesium salt and/or a calcium salt" as required by present claim 25 and dependent claims thereof. The Wiedmann et al. reference fails to cure this deficiency.

Applicants submit further that none of the Malvolti et al. reference or the Wiedmann et al. reference or the combination thereof teach or suggest the preparation as claimed in claim 25, wherein "the preparation contains a magnesium salt and/or a calcium salt", as required by claims 27 and 28 and 31-33.

In view of the above, Applicants respectfully request withdrawal and reconsideration of the rejection.

With reference now to the final 103(a) rejection over Malvolti et al. and further in view of Azria et al. (U.S. 5,7597,565), the following remarks are offered.

Applicants traverse the rejection.

Azria et al. was discussed in Applicants response to the Office Action dated July 3, 2007.

As discussed above, the Malvolti et al. reference, either alone or in combination, fails to teach or suggest the invention as recited in present claim 25 and dependent claims thereof. The Azria et al. reference fails to cure this deficiency. That is, the

combination of Malvolti and Azria do not teach or suggest the invention recited in claim 34.

For all of the foregoing reasons, Applicants respectfully request reconsideration and withdrawal of the rejections.

In view of the above amendments and remarks, Applicants believe the pending application is in condition for allowance.

REQUEST FOR EXTENSION OF TIME AND FEE AUTHORIZATION

Applicant hereby requests a one-month extension of time for filing the within response. Please charge all fees associated with the extension and any other required fee (or credit any overpayment) to Deposit Account No. 04-1105, Reference No. 65177(45107).

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Respectfully submitted,

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